REMARKS/ARGUMENTS

Claims 34 – 36 and 38 – 50 are pending in the application. Claims 46 – 50 were withdrawn as drawn to a non-elected invention, pursuant to a restriction requirement. Claim 37 was canceled by a previous Amendment. Claims 34 and 36 are amended by the present Amendment. No new matter is added.

Only and merely in order to expedite the allowance of the patent, Applicants have amended claim 34 and claim 36, even if, in the Applicants' view said amendments are not necessary.

Claim 36 is rejected under 35 U.S.C. §112, 1st paragraph (written description) regarding the term "cellulose derivatives."

In claim 36, the term "cellulose derivatives" has been deleted to overcome the written description rejection, even though Applicants respectfully disagree with the Examiner's position in this matter.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the §112, 1st paragraph rejection to claim 36.

Claims 34 – 36, 38 – 42 and 44 are rejected under 35 U.S.C. §103(a) over Kanios (U.S. 2002/0004065) (hereinafter, "Kanios").

Claim 34 now recites:

> "34. A device for controlled local delivery of rifaximin, comprising between 0.5 wt% and 30 wt% rifaximin and a bi-phasic material, wherein in said bi-phasic material the solid phase is an elastic polymeric matrix comprising polyvinylalcohol, and the liquid phase is water that fills up the pores of said matrix, thereby avoiding an intense red color from rifaximin at the site of administration." [emphasis added]

where the underlined phrase has been introduced in order to further point out the differences between the current invention and the cited prior art, Kanios, as discussed below. This amendment finds antecedent in paragraph 0007 of the description.

Applicants first note that the meanings of the terms "local," "topical," and "transdermal" indicate the differences between the present invention and Kanios. In this regard, the definitions of these terms from the Merriam-Webster Dictionary are attached in **Annex A**.

In this context, "local" and "topical" have similar meanings and are used as synonyms:

Definition of LOCAL

4 : involving or affecting only a restricted part of the organism : TOPICAL <a *local* anesthetic>

Definition of TOPICAL

2 : designed for or involving local application and action (as on the body) <a *topical* anesthetic> <a *topical* remedy>

whereas "transdermal" has a completely different meaning:

Definition of TRANSDERMAL

: relating to, being, or supplying a medication in a form for absorption through the skin into the bloodstream <*transdermal* drug delivery> <*transdermal* nitroglycerin> <*transdermal* nicotine patch>

Therefore, as far as the routes of drug administration are concerned, the term "transdermal delivery" is expressly understood to involve the diffusion of the drug through the skin and ultimately absorption into the systemic circulation, while "topical delivery" and "local delivery" simply mean that a medication is applied to body surfaces, such as the skin or mucous membranes, and that the action is at said surfaces' portion.

The device of claim 34 is for the local delivery of rifaximin, i.e. the rifaximin is a nonsystemic antibiotic and the effect of the same is localized and limited to the skin/mucosae

surfaces portion of contact and neighboring areas, where the device is placed. This is clear throughout the pending application.

Kanios, as explained in the previous responses, discloses **transdermal** drug **delivery** systems, as clearly shown in its Title, Abstract, Field of the Invention, Background of the Invention, Summary of the Invention, Brief Description of Drawings, Detailed Description of the invention, Examples and Claims.

Applicants respectfully submit that a skilled person would not have considered a document limited to **transdermal systems** for solving a technical problem of a **nonsystemic antibiotic**.

In the previously submitted response, the Applicants provided documents demonstrating the nonsystemic nature of rifaximin, one of them being an **official Report about rifaximin** issued by the *Committee Veterinary Medicinal Products* of the *European Agency for the Evaluation of Medicinal Products* (EMEA).

In the outstanding Office Action, the Examiner alleged:

> that topical application resulted in rifaximin being present in the skin but not in the muscle and fat underlying the treatment areas. These are insufficient to indicate that no skin penetration occurs. Substances can pass through the skin and either because of insufficient quantity or because the substance is not transported far enough into the skin to reach the circulatory system so that such agents can be transdermally absorbed but not be detected in either the blood or urine. In the absence of evidence regarding the ability of rifaximin to pass through the skin by more direct experiments with greater detail as tow hat was essayed, this line of argument is unpersuasive. It is also noted that the preamble of the claim only requires local delivery and not systemic delivery.

Applicants respectfully disagree with these arguments for the following reasons.

The fact that "the topical application resulted in rifaximin being present in the skin but not in the muscle and fat underlying the treatment areas" matches exactly the above given definition of topical administration of a non-systemic antibiotic, where the action is only local,

i.e., at the skin/mucosae surfaces portion of contact and neighboring areas thereof: therefore, this includes skin penetration but expressly excludes further diffusion of rifaximin to deeper areas and even more so to the bloodstream, since rifaximin is a well known non-systemic antibiotic.

To further support the non-absorbability via-transdermal administration of rifaximin, Applicants hereby provide a number of publications where said non-systemic absorbability of rifaximin has been shown.

Annex B: US 4,341,785 is the basic patent of rifaximin, where this compound was first disclosed and prepared (see Example 6).

At column 4, line 67, to column 5, line 13, it is stated that rifaximin is "scarcely absorbed from animal organs and tissues when administered by oral route, and is found unaltered in the stool in a remarkable percentage with respect to the administered dosage." Therefore, the non-absorbability of rifaximin was known since 1980 (see priority date). As a matter of fact, it should be noted that the results shown in this patent are for oral administration, where the absorbability by tissues and organs is maximum. Thus, it should be considered that, since the skin is a physiological barrier that is greatly higher than mucosae and internal tissues, the absorbability of rifaximin after topical/local administration on the skin surface is consequently and easily understood to be even more reduced, so that the transdermal diffusion to the bloodstream is *de facto* prevented.

Annex C: Venturini et al. "Transcutaneous absorption of a topical rifamycin preparation: rifaximin (L/105)," Drugs Exp Clin Res. 1987; 13(4):231-2.

This publication in 1987 demonstrated that "contrary to what was observed for rifampicin, Rifaximin was practically not absorbed." As a matter of fact, in the section Discussion, the authors affirm that:

> Rifaximin is practically not absorbed after topical cutaneous application: in fact it was not possible to detect concentrations of Rifaximin near the sensitivity limit of the analytical procedure (0.2 mcg/ml)

Therefore, this confirms that the diffusion of rifaximin is hindered by the skin as a physiological barrier, and consequently rifaximin is definitely a non-systemic antibiotic.

Annex D: Parini et al. (abstract) "Effect of rifaximin and paromomycin in the treatment of portal-systemic encephalopathy," Current Therapeutic Research, Volume 52, Issue 1, July 1992, Pages 34-39.

This abstract further confirms that rifaximin is defined as "new non-absorbable antibiotic" even in this case of treatment of portal-systemic encephalopathy, where the administration was an oral administration.

Annex E: Prasad et al. "In vitro activity of rifaximin, a topical rifamycin derivative, against Chlamydia trachomatis," Diagnostic Microbiology and Infectious Disease, Volume 16, Issue 2, February 1993, Pages 135-136.

This publication affirms that also in the case of bacterial vaginosis, rifaximin can be successfully used as non-absorbable topical agent:

> Rifaximin has been shown to exhibit a good spectrum of activity against organisms associated with bacterial vaginosis (Hoover et al., 1992). Because of this spectrum and the drug's poor absorption it may be a potential topical agent for the treatment of bacterial vaginosis. In topical form (2%–5% concentration), drug concentrations in the range of 20,000–50,000 μg/ml would be achieved, several times higher than those routinely tested in vitro. If rifaximin is tested in bacterial vaginosis and other localized genital tract infections, then it would obviously be desirable if it had activity against the most common genital pathogens. In our evaluation rifaximin exhibits considerable in vitro activity against clinical and laboratory isolates of *C. trachomatis*. These results suggest that topical rifaximin may be a promising agent to treat local genital tract infections.

Annex F: Hoover et al. "Antimicrobial activity and spectrum of rifaximin, a new topical rifamycin derivative," Diagn. Microbiol. Infect. Dis. 1993 Feb; 16(2):111-8.

Also in this publication, rifaximin is defined to be suitable for topical treatment of bacterial vaginosis, similarly to what was assessed in the previous document.

Annex G: Palazzini et al. "Treatment of pyogenic skin infections with rifaximin cream," Riv. Eur. Sci. Med. Farmacol., 15(2):87-92 (1993)

This publication regards the topical application of a cream containing rifaximin for treating pyogenic skin infections. On page 87, last two paragraphs, it is stated:

> Since it is not absorbed by the gastrointestinal mucosa, Rifaximin was used for the oral treatment of various intestinal infections including bacterial diarrhea[6,7] or maintenance therapy in the case of systemic encephalopathy[8,9] and in the prevention and treatment of septic complications after surgery on the large intestine[10,11].
>
> The non-absorption at a systemic level appeared to be useful in the local treatment of skin infections from pyogenic germs, since the novelty of the molecule and its kinetic features could, in our opinion, form the basis of an effective local treatment without negative reactions.

Therefore, also in this case, it has been confirmed that rifaximin is not absorbed at a systemic level after topical skin application.

Annex H: Berlö et al. "A prospective study in healthy volunteers of the topical absorption of a 5% rifaximin cream," Drugs Exp. Clin. Res. 1994; 20(5):205-8.

Also this publication regards the topical application of a cream containing rifaximin for treating skin infections, where it is stated that "in animals, no absorption was detected after topical application on the skin" and "the results confirm studies performed in animals which showed that rifaximin is not absorbed and is well tolerated" (see abstract). On page 207, last paragraph of the Discussion, it is further concluded that:

> The present findings thus confirm what has been reported in previous work, i.e., that rifaximin cannot be detected in plasma and urine samples after topical (percutaneous) application.

Annex I: Scarpignato et al. "Rifaximin, a poorly absorbed antibiotic: pharmacology and clinical potential," Chemotherapy 2005; 51:36-66.

This publication is a review focused on rifaximin, where on page 42, in the paragraph "In vivo activity" it is stated:

> The lack of absorption and, consequently, the lack of 'systemic' therapeutic activity was also demonstrated in a model of experimental tuberculosis in the guinea pig [75]. Here again, oral rifampicin but not oral rifaximin did protect the animals from the development of the infection (table 3) [76].

Annex J: Adachi et al. "Rifaximin: A Novel Nonabsorbed Rifamycin for Gastrointestinal Disorders," Reviews of Anti-Infective Agents, 2006:42 (15 February), 541-547.

Even if this document refers to treatment of Gastrointestinal Disorders by oral administration of rifaximin, however, also in this case, it can be found that rifaximin is once again defined as follows (see page 545, right column):

> "The only contraindication of rifaximin use is history of hypersensitivity to a rifamycin drug [3]. Because of its lack of absorption, rifaximin should be safe for use in the pediatric population and in pregnant and breastfeeding women."

Annex K: Taylor et al. "Rifaximin, a Nonabsorbed Oral Antibiotic, Prevents Shigellosis after Experimental Challenge," Clin. Infect. Dis. (2006) 42 (9): 1283-1288.

Even if this document refers to oral administration of rifaximin, it is remarked that:

> The availability of rifaximin, an oral nonabsorbe antibiotic introduced in 2004 in the United States fo the treatment of travelers' diarrhea, has renewed inter est in chemoprophylaxis of travelers' diarrhea. Rifaxi min is well tolerated [11], does not appear to induc resistance in enteric flora during repeated dosing [12]

Thus, it is once again confirmed the non-absorption of rifaximin.

Annex L: Weinstock "Irritable Bowel Syndrome: Emergence of New Diagnostic and Treatment Options," 2009.

The author of this publication is Dr. Weinstock, on the speakers bureau for Salix Pharmaceuticals, Inc., that on Oct. 25, 2002 announced that it has received an approvable letter from the U.S. Food and Drug Administration (FDA) for the New Drug Application (NDA) for rifaximin, at that time, an investigational drug under review for the treatment of travelers' diarrhea.

In this document, the author defines rifaximin as a nonsystemic antibiotic, as also reported in Table 2, page 18.

Annex M: Cottreau et al. "Rifaximin: a nonsystemic rifamycin antibiotic for gastrointestinal infections," Expert Review of Anti-infective Therapy, July 2010, Vol. 8, No. 7, Pages 747-760.

Even if also this document refers to oral administration of rifaximin, it is noteworthy that rifaximin is still defined as nonsystemic antibiotic also to date.

All the documents (Annexes B - M) herein provided demonstrate that the rifaximin is a very well known non-systemic and non-absorbable antibiotic from 1980 to date, independently of the administration route.

Consequently, the Examiner's argument that "Substances can pass through the skin and either because of insufficient quantity or because the substance is not transported far enough into the skin to reach the circulatory system so that such agents can be transdermally absorbed but not be detected in either the blood or urine." (page 6 of Office Action) is contrary to all the evidence presented in the above publications, as well as in the official Report about rifaximin issued by the *Committee Veterinary Medicinal Products* of the *European Agency for the Evaluation of Medicinal Products* (EMEA).

Furthermore, the Office Action subsequently also affirms: "In the absence of evidence regarding the ability of rifaximin to pass through the skin by more direct experiments with greater detail as to what was assayed, this line of argument is unpersuasive. It is also noted that the preamble of the claim only requires local delivery and not systemic delivery"; however, the current application never cites "systemic delivery," but indeed the contrary (see par. 0004), providing an additional reason that Kanios does not apply to the present disclosure.

Applicants wish to point out that the current invention regards a device for controlled local delivery of rifaximin avoiding the rifaximin intense red color at the site of administration, thus allowing the use of rifaximin, e.g. in the oral cavity as well as on the skin, even at high concentrations, as clearly reported at paras. 0003-0004 of the current application. In fact, for

aesthetic reasons, the problem of intense red color prevents its use in all those places, like the mouth or skin, where the patient wishes to maintain a socially acceptable aspect.

Conversely, Kanios discloses devices for transdermal delivery of active agents. Accordingly, not only are the field of endeavours different, but also a scientifically incorrect teaching is given when Rifaximin is listed within the possible active agents transdermally deliverable.

Thus, when applying the Graham inquiries for establishing a background for determining obviousness, particularly the first inquiry, i.e. "*Determining the scope and the contents of the prior art*," the Office Action does not consider that the state of the art as a whole concerning rifaximin, starting from its first disclosure on 1980, coherently and uniformly proved and affirmed the non-systemic absorbability of this specific antibiotic, either when oral administered or when applied to the skin, which is the most effective physiological barrier of the body.

This was specially assessed in the above-mentioned **Annex C** dated 1987, where it was demonstrated that, after a topical skin application of a preparation containing Rifampicin and a preparation containing Rifaximin, Rifaximin was not absorbed, contrary to what was observed for Rifampicin.

Reminding that the only point where Kanios cites Rifaximin is the following paragraph:

> **[0093]** Ansamycins such as Rifamide, Rifampin, Rifamycin and Rifaximin;

where Rifampin is the USAN (United States Adopted Name) of Rifampicin, it becomes clear that **Kanios** is absolutely scientifically incorrect and undeniably unreliable.

It should be reminded that ascertaining the scope and content of the prior art means evaluating all of the prior art and not just the prior art that supports a finding of obviousness.

This means that, at the time the invention was made, the skilled person was well aware of the fact that Rifaximin can not be transdermally administered and accordingly would have never taken Kanios into consideration at all.

Additionally, Applicants also respectfully disagree with the application of the second Graham inquiry, i.e., "*Ascertain the differences between the claimed invention and the prior art*," in the Office Action.

As a matter of fact, not only did the Office Action consider Kanios relevant and reliable prior art by disregarding the actual teaching of the state of the art as a whole, but also disregarded the actual teaching of the current invention as a whole.

In fact, understanding the invention as a whole means placing the invention into the broader context of what the invention accomplishes in relation to what the art as a whole teaches. In this regard, consideration whether the invention addresses a technical problem never noticed before in the art is part of understanding the invention as a whole. In fact, the primary locus of inventive activity is the discovery of the problem itself and possible sources thereof. It follows that a never cited technical problem, i.e. the intense red color preventing the external use of rifaximin, a never cited source of the same, i.e. "rifaximin in the form of small crystals generates a peak of concentration, at the moment of the application but then it disperses itself quickly far away from the point where it is placed losing its effectiveness," a surprising solution nowhere suggested, i.e. the claimed device, necessarily lead to a patentable invention.

In view of all the above arguments, it can be summarized, also including Applicants' previous responses, that:

- Kanios is in the field of transdermal delivery of drugs, whereas the current invention in the field of **local administration of non-systemic rifaximin**;

- Kanios gives **a scientifically incorrect teaching, when including Rifaximin in the list of transdermally deliverable drugs**, thus the skilled person would have definitely disregarded the document as a whole as **incorrect and absolutely unreliable**, also in view of the Annexes herewith enclosed;

- the Office Action incorrectly applies Graham inquiries 1 and 2, as well as subsequent inquiries 3 and 4, thereby drawing incorrect conclusions;

- even if hypothetically considered, in view of the fact that, contrary to Kanios, all the

cited Annexes teach the non-systemic absorbability of Rifaximin, Kanios represents a teaching away for the skilled person that would have never considered enabling the Kanios devices.

Accordingly, Applicants respectfully submit that the conclusions in the Office Action are a hindsight reconstruction of the claimed invention, by having knowledge of the same. As a matter of fact, the Office Action isolated substances from said unlimited lists in Kanios in order to conveniently lead to the claimed invention, while unacceptably disregarding the actual teaching of the prior art as a whole and the actual teaching of the invention as a whole.

In view of the arguments above, Applicants submit that the Office Action made an improper reconstruction of the claimed invention, since conversely it does not take into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and included knowledge gleaned only from the Applicants' disclosure, at the same time relying all the raised rejections only on a scientifically incorrect teaching of Kanios.

For all the above reasons, Applicants submit that claim 34 is not obvious over Kanios, and the rejection under 35 U.S.C. §103(a) should be withdrawn accordingly.

Likewise, for at least the same reasons as presented above for independent claim 34, Applicants further submit that dependent claims 35, 36, 38 – 42, and 44 are also not obvious over Kanios, and respectfully request reconsideration and withdrawal of the §103(a) rejections to these claims as well.

Claims 34 – 36 and 38 – 44 are rejected under 35 U.S.C. §103(a) over **Kanios** further in view of **Govil et al.** (U.S. 4,908,213) (hereinafter, "Govil").

Kanios is described in detail above. Govil, as described in previous responses, discloses a transdermal drug delivery patch for transdermal delivery of nicotine as an aid for smoking cessation. In view of the present Amendment, as well as the Annexes and discussion above differentiating the claims over Kanios, Applicants submit that Govil, taken alone or in

combination with Kanios, fails to disclose or suggest all of the features in claim 34, and its dependent claims 35, 36, and 38 – 44.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejections to claims 34 – 36 and 38 – 44 over the combination of Kanios and Govil.

Claims 34 – 36, 38 – 42, 44 and 45 are rejected under 35 U.S.C. §103(a) over **Kanios** in view of **Wharton** (U.S. 6,194,455) (hereinafter, "Wharton").

The relevant portions of Kanios are described above. Briefly, Wharton discloses a composition and method for treating skin ulcers with sucralfate in combination with a topical anesthetic in a particular formulation. However, for the reasons set forth in the previous responses, the composition and method disclosed in Wharton fail to supplement the deficiencies described above for Kanios with respect to claim 34 or its dependent claims. Therefore, Applicants submit that Wharton, taken alone or in combination with Kanios, fails to disclose or suggest the features in claims 34 – 36, 38 – 42, 44 and 45.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejections to claims 34 – 36, 38 – 42, 44 and 45 over the combination of Kanios and Wharton.

For all of the above reasons, Applicants submit that the device, as set forth in claim 34 and in dependent claims 35, 36, and 38 – 45, is not obvious over the cited prior art documents, either taken alone or combined with each other.

Therefore, Applicants respectfully submit that the application as currently pending is in condition for allowance, on the grounds that the arguments provided fully overcome the rejections raised in the Office Action.

Respectfully submitted,

2/4/11
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